Hydroboration of the Benzomorphan-borane (II)——An excess of diborane was introduced into a solution of II (1.37 g.) in THF (30 ml.) in the same manner as described previously. The reaction mixture was oxidized and worked up in the like manner to give the 9β-hydroxymethyl derivative (350 mg., 21.6%) along with the 9α-hydroxymethyl derivative (20 mg., 1.4%). The neutral product weighed 350 mg., m.p. 126~132° and was identified with A by IR spectral comparison.

Attempted Isolation of Alkylborane Intermediates——I (1.2 g.) in THF (25 ml.) was hydroborated with an excess of diborane in the same manner as described previously. The reaction mixture was treated cautiously with H_2O to decompose excess diborane and extracted with Et_2O. Evaporation of dried Et_2O solution gave gum (1.25 g.) which was dissolved in benzene and chromatographed over a silica gel column. Elution with benzene-Et_2O (1:1) gave A (520 mg.), m.p. 130~133°. Other fractions failed to give crystalline product.

The authors express their gratitude to Dr. E. L. May, National Institutes of Health, U. S. A. for encouragement and information on benzomorphans and to Dr. N. Sugimoto of this laboratory for his interest and encouragement throughout this series of works. They also thank Dr. K. Kotera for IR spectra and Mrs. F. Hisamichi and Mr. T. Kono for microanalyses.

Summary

The stereochemical course of the borane addition to 9-methylenebenzomorphan leading to the 9β-hydroxymethyl derivative was further examined.

Formation of the intramolecular coordinated amineborane (A) was observed by the reaction of diborane with both the free amine (I) and the benzomorphan-borane (II). That the first one mole of boron hydrides adds to I at the nitrogen to give the amine-borane (II) without addition to the double bond was also established. Isolation of intermediates in alkylborane stage was attempted.

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162. Yasuo Inubushi, Hisashi Ishii, Bompei Yasui, Takeshi Konita, and Takashi Harayama : Isolation and Characterization of Alkaloids of the Chinese Drug "Chin-Shih-Hu."*1

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The Chinese drug "Chin-Shih-Hu" (Japanese name "Kin-Sekkoku") has been used as a tonic and antipyretic. There has been some uncertainty about the plant from which the drug was originally prepared but Kimura[1] and Suzuki, *et al.*[2] reported that it was probably *Dendrobium nobile* LINDL.

With regard to its basic components Suzuki, *et al.*[2] reported that they isolated a new alkaloid from this drug, which they called dendrobine, m.p. 134°, $[\alpha]_D^{16}$ −51.5° (c=1.0, EtOH), in 1932. They also showed that dendrobine has the molecular formula $C_{16}H_{25}O_2N$,

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*1 A preliminary communication on the structure of dendrobine appeared in Yakugaku Zasshi, **83**, 1184 (1963); for a full report, see Tetrahedron, **20**, 2007 (1964). Cf. T. Okamoto, *et al.*: This Bulletin, **12**, 506 (1964). Y. Hirata, *et al.*: Tetrahedron Letters, No. 2, 79 (1964).

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1) K. Kimura : Bulletin of the Shanghai Science Institute, **6**, 1 (1936); *Ibid.*, **7**, 11 (1937).

2) H. Suzuki, I. Keimatsu, K. Ito : Yakugaku Zasshi, **52**, 1049 (1932); *Ibid.*, **54**, 801 (1934).

containing a N-methyl group and no double bond, and that the oxygens are present as a γ-lactone.

Since then there have been no reports on further details of the structure of dendrobine and this prompted us to elucidate its structure.

In 1961 a few kilograms of the drug first came on to the drug market in Hong Kong, but as Suzuki, *et al.*[2] pointed out, many kinds of so-called "Chin-Shih-Hu" with very similar superficial appearances appear on the market. Preliminary alkaloid tests on these drugs showed that some of them contained only negligible amounts of alkaloid and only a few samples contained appreciable amounts, but these samples could not be distinguished by their appearance. Thus we had much trouble in getting the required material. Fortunately, at the end of 1962, we obtained rather large quantities of suitable samples for isolating dendrobine and these samples were extracted and the basic components were separated.

As a result, we isolated a crystalline alkaloid of m.p. 134.5~136°, which, though it was not compared directly with an authentic sample of dendrobine, was assumed to be identical with dendrobine on the basis of the results of elemental analyses and comparison the physical constants of the isolated base and its derivatives with those of dendrobine and its derivatives.[2] Two other alkaloids were also isolated. This paper reports on the isolation and characterization of these alkaloids.

The finely-cut samples of the chinese drug were extracted with methanol and the basic components were separated into the tertiary alkaloids and the water soluble

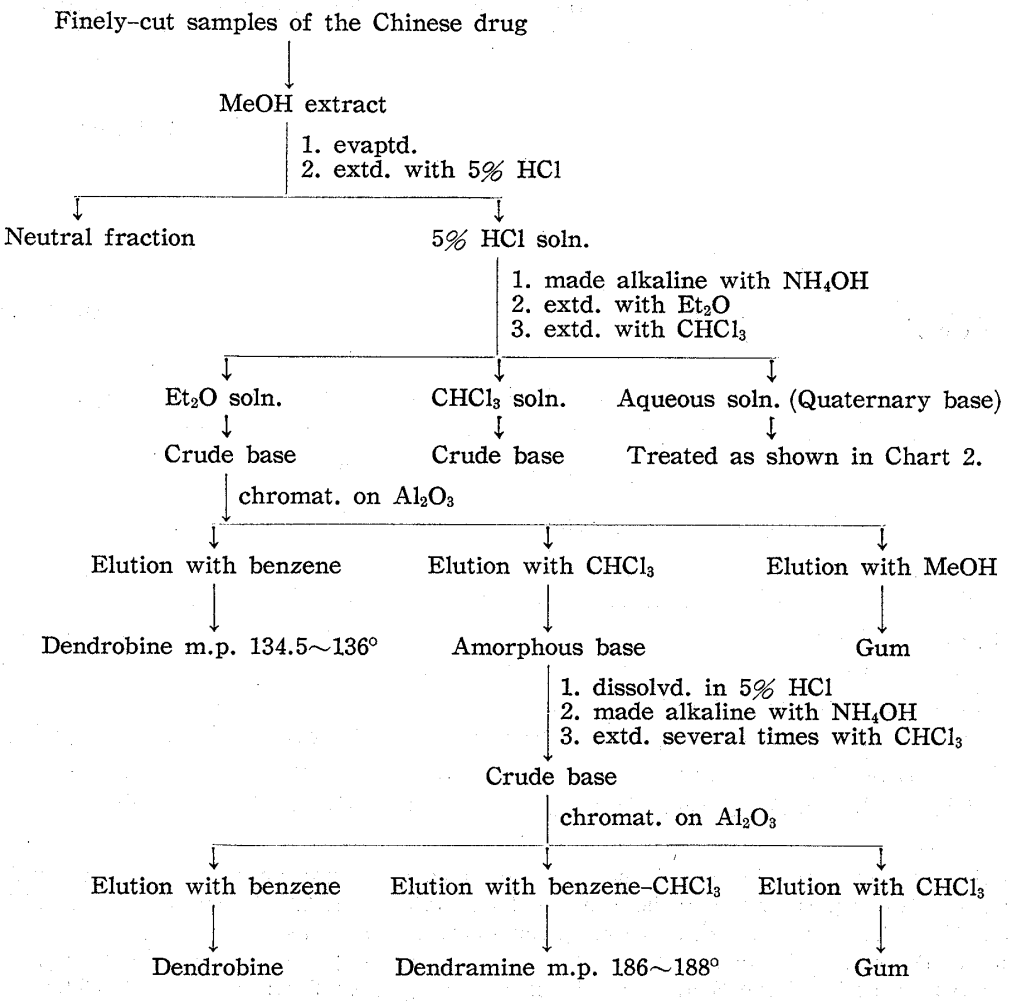

Chart 1. Isolation of Tertiary Bases of "Chin-Shih-Hu"

quaternary base, as shown in Chart 1. The crude tertiary bases were purified chromatographically on alumina and elution of the column with benzene gave dendrobine, m.p. 134.5~136°, $[\alpha]_D^{14}$ −48.4° (c=1.89, MeOH). The analytical values of these crystals showed that their composition was $C_{16}H_{25}O_2N$. Dendrobine has the following spectroscopic properties: IR cm^{-1}: $\nu_{C=O}$ 1767 (KBr), 1763 ($CHCl_3$) (γ-lactone); NMR*[3] 9.00~9.04 τ (6H), two doublets (an isopropyl group or two >CH–CH_3 groups); 8.67 τ (3H) singlet (≥C–CH_3), 7.51 τ (3H) singlet (N–CH_3); 5.20 τ (1H) quartet (–CO–O–CH<).

The crude base eluted from the column with chloroform was purified by repeated chromatography on alumina and elution with benzene gave dendrobine. Continued elution of the column with the same solvent resulted in the appearance of material which formed needles, m.p. 186~188°, $[\alpha]_D^4$ −27° (c=1.6, MeOH) with the molecular formula $C_{16}H_{25}O_3N$. The spectroscopic properties of this material were as follows. IR cm^{-1}: ν_{O-H} 3120 (broad); $\nu_{C=O}$ 1779 (Nujol) (γ-lactone); NMR 8.90~9.10 τ (6H) triplet (an isopropyl or two >CH–CH_3 groups); 8.68 τ (3H) singlet (≥C–CH_3), 8.02 τ singlet (disappeared on treatment with D_2O) (hydroxyl group), 7.56 τ (3H) singlet (N–CH_3), centered at 5.21 τ (1H)

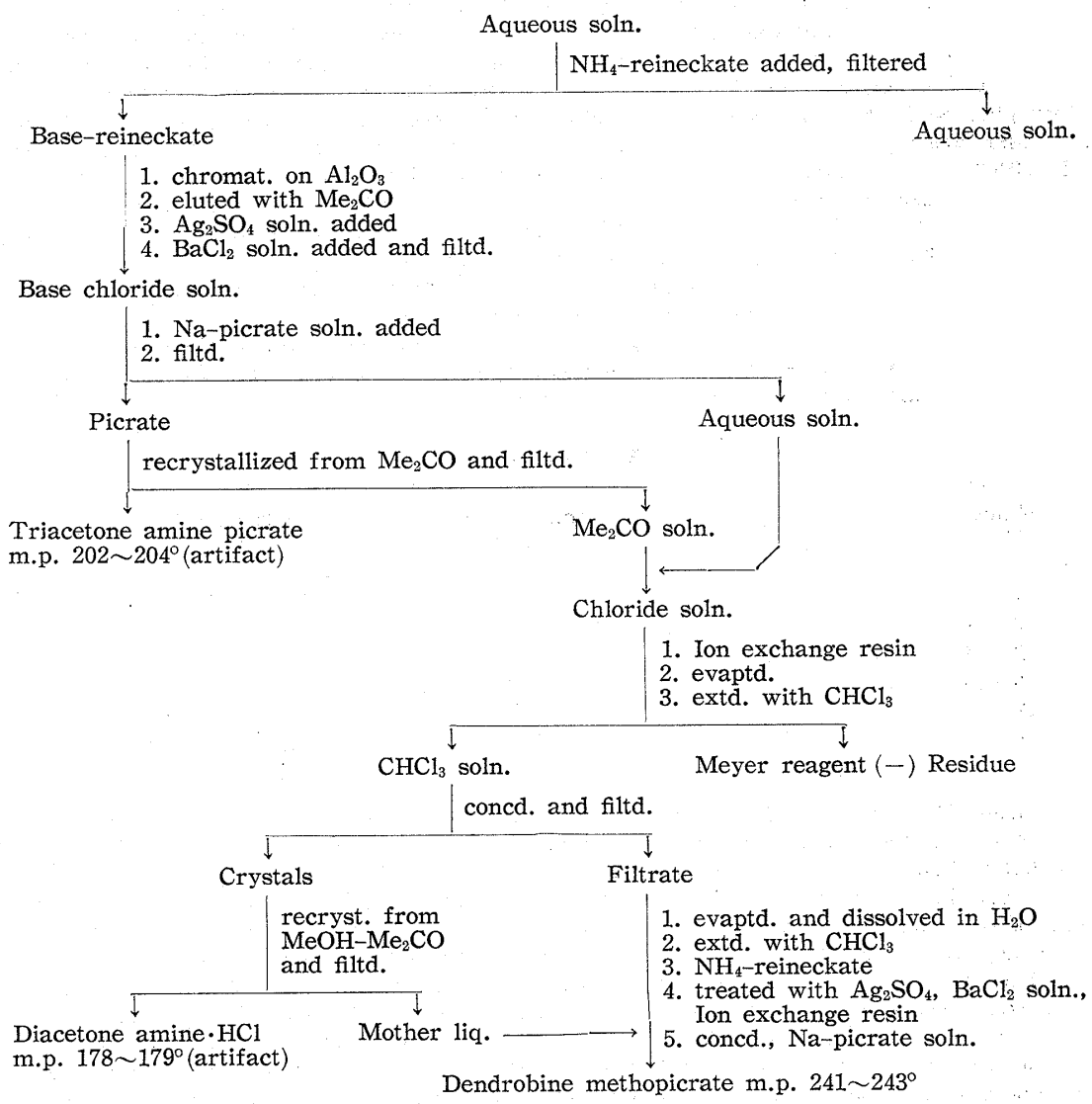

Chart 2. Isolation of the Quaternary Base

*[3] NMR spectra were measured on a Varian A-60 Spectrometer in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard.

diffuse quartet (-CO-O-CH〈). This alkaloid has not been reported previously in chemical literature and it was named dendramine.

The quaternary base in the aqueous layer separated from the tertiary bases by extraction as described above was isolated and purified by precipitation as a reineckate, as shown in Chart 2. Consequently, a crystalline picrate, m.p. 241~243° with the molecular formula $C_{17}H_{28}O_2N^+ \cdot C_6H_2O_7N_3^-$ was obtained. A γ-lactone grouping in its molecule was shown by its infrared spectrum (1780 cm^{-1}), (Nujol). The identity of this picrate with an authentic sample of dendrobine methopicrate, m.p. 240~242° which in turn was derived from dendrobine through its methiodide, was achieved by comparison of infrared spectra and mixed melting point determination. From the foregoing results it is concluded that the quaternary alkaloid found in the Chinese drug "Chin-Shih-Hu" is the N-methyl-dendrobium salt.

Experimental*4

Extraction of "Chin-Shih-Hu"——A finely-cut sample (1.2 kg.) was soaked in MeOH (8 L.) for 2 days; the extract was separated from the residue and the latter was then reextracted four times with boiling MeOH (each 5 L.). The extracts were combined and concentrated to a blackish brown residue (148 g.) under reduced pressure. The residue was extracted several times with 5% aq. HCl until the acid extract showed a negative reaction with Meyer's reagent. The combined acid extracts were filtered, shaken thoroughly with Et_2O to remove acidic and neutral substances and brought to pH 11.0 by addition of NH_4OH under cooling with ice. Then, the alkaline solution was extracted exhaustively with Et_2O followed by $CHCl_3$. The Et_2O and $CHCl_3$ extracts were combined and evaporated to dryness. The residue was again dissolved in 5% aq. HCl, made alkaline (pH 11.0) with NH_4OH and extracted with Et_2O followed by $CHCl_3$. The Et_2O and $CHCl_3$ extracts were each dried over anhyd. Na_2SO_4 and evaporated to leave 3.9 g. and 0.26 g. of crude bases, respectively.

From the aqueous alkaline solution separated from the tertiary bases by extraction with Et_2O and $CHCl_3$ the quaternary base was isolated and purified as shown in Chart 2.

Isolation and Characterization of Tertiary Bases——The benzene solution of the crude tertiary bases (0.56 g.) obtained from the Et_2O extracts was chromatographed on alumina (6 g.). Successive elution with benzene, $CHCl_3$ and MeOH gave the following fractions.

Table I.

Fract. No.	Solvent	Volume of solvent (ml.)	Eluted product (g.)
1	benzene	10	—
2~11	〃	97	0.49 (m.p. 134~136°)
12~14	〃	20	—
15~16	$CHCl_3$	40	0.09 (amorphous base)
17	〃	30	—
18~19	MeOH	100	Gum

Dendrobine——Fraction Nos. 2~11 gave colorless crystals which melted at 134~136°. Repeated recrystallization from Et_2O did not change the melting point. *Anal.* Calcd. for $C_{16}H_{25}O_2N$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.85; H, 9.81; N, 5.32.

Isolation and Characterization of Dendramine——On chromatography of the crude tertiary bases on alumina, elution with $CHCl_3$ gave an amorphous base with an IR spectrum suggesting the presence of a hydroxyl group. A solution of the bases (5 g.) in benzene was shaken several times with 5% HCl until the acid extract showed a negative reaction with Meyer's reagent. The acid extracts were shaken with Et_2O to remove acidic and neutral substances, made alkaline with conc. NH_4OH and the alkaline solution was extracted exhaustively with Et_2O. The Et_2O extracts were combined, dried over anhyd. Na_2SO_4 and on evaporation of the solvents 3.85 g. of amorphous bases were obtained which were again chromatographed on alumina. Successive elution with benzene, $CHCl_3$ and MeOH gave the following fractions.

*4 All melting points were observed on a Kofler microscopic hotstage and are given as uncorrected values.

Table II.

Fract. No.	Solvent	Volume of solvent (ml.)	Eluted product (g.)
1	benzene	80	0.3 (dendrobine)
2～4	〃	240	amorphous base
5	〃	80	—
6	$CHCl_3$	150	amorphous base

The amorphous base collected from fraction Nos. 2～4 was rechromatographed on neutral alumina and elution with benzene gave the following fractions.

Table III.

Fract. No.	Volume of solvent (ml.)	m.p. (°C)	Eluted product
1～3	3×50	134	0.32 g. (dendrobine)
4～5	2×50	143～160	
6～7	2×50	178～185	20 mg.
8～9	2×50	178～185	

The crystalline base collected from fraction Nos. 6～9 was recrystallized from a small amount of Et_2O to colorless needles which melted at 186～188°. *Anal.* Calcd. for $C_{16}H_{25}O_3N$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.47; H, 8.94; N, 4.89.

Isolation and Characterization of Quaternary Base (Dendrobine methopicrate)——The alkaline aqueous layer remaining after extraction with Et_2O and $CHCl_3$ was acidified with AcOH and satd. aqueous NH_4-reineckate solution was added until no further precipitation occurred. The reineckate of the quaternary base was collected by filtration, dried in air, dissolved in Me_2CO and chromatographed on alumina. The reineckate of the quaternary base eluted from the column with Me_2CO was decomposed with Ag_2SO_4 and then converted to the chloride. The solution of chloride separated from the precipitates of Ag-reineckate and $BaSO_4$ by filtration was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of H_2O. Addition of aq. sodium picrate to the solution of the chloride gave a yellow crystalline precipitate which was collected by filtration. Recrystallization from Me_2CO gave yellow prisms which melted at 202～204°. IR cm^{-1}: $\nu_{C=O}$ 1704, 1686 (Nujol). *Anal.* Calcd. for $C_9H_{17}ON^+ \cdot C_6H_3O_7N_3^-$: C, 46.87; H, 5.25; N, 14.58. Found: C, 47.20; H, 5.13; N, 14.32. This picrate was proved to be identical with an authentic sample of triacetone amine picrate by comparison of IR spectra and mixed melting point determination. From the above chromatographic treatment this picrate would be an artifact.

The filtrate from which the triacetone amine picrate was separated by filtration and the mother liquor after the recrystallization of the triacetone amine picrate were combined and the picrate of the quaternary base was converted to its chloride in the usual manner. The solvent was evaporated off to leave a viscous oil which could not be induced to crystallize. A solution of this residue in H_2O adjusted to pH 7.0～8.0, was passed through a column of ion-exchange resin (Amberlite IRC-50, RH type). To remove NH_4Cl, the column was washed with distilled H_2O until washings gave no Nessler's reaction, and the material was eluted with 0.5*N* HCl. The acidic solution, including the quaternary base chloride, was evaporated to dryness under reduced pressure and the residue was extracted thoroughly with $CHCl_3$. The $CHCl_3$ solution was concentrated to give a precipitate which was collected by filtration. Recrystallization from MeOH-Me_2CO gave 610 mg. of colorless prisms, m.p. 178～179°. IR cm^{-1}: $\nu_{C=O}$ 1709, $\nu_{\overset{+}{N}-H}$ 2558 (Nujol). *Anal.* Calcd. for $C_6H_{13}ON \cdot HCl$: C, 47.53; H, 9.31; N, 9.24. Found: C, 47.34; H, 9.44; N, 9.14. This hydrochloride was proved to be identical with a sample of synthetic diacetone amine hydrochloride by comparison of IR spectra and mixed melting point determination. From the above treatments this hydrochloride would, also, be an artifact.

The filtrate from which diacetone amine hydrochloride was removed, and the mother liquor after the recrystallization of the diacetone amine hydrochloride were combined, made alkaline with NH_4OH and extracted with $CHCl_3$. The aqueous layer was again acidified with AcOH and the quaternary base was collected as the reineckate which was then decomposed with Ag_2SO_4 and converted to the chloride. The chloride solution was passed through a column of the same ion-exchange resin as used above. The eluate of the chloride solution was concentrated and a saturated aqueous solution of sodium picrate was added. The crystalline yellow precipitate was collected by filtration and recrystallization from

MeOH yielded 100 mg. of yellow prisms which melted at 241~243°. IR cm^{-1}: $\nu_{C=O}$ 1780 (Nujol). *Anal.* Calcd. for $C_{17}H_{28}O_2N^+ \cdot C_6H_2O_7N_3^-$: C, 54.53; H, 5.97; N, 11.06. Found: C, 54.43; H, 5.91; N, 10.94. By comparison of IR spectra and mixed melting point determination this picrate was identified with a sample of dendrobine methopicrate derived from dendrobine.

Dendrobine Methopicrate from Dendrobine——To a solution of dendrobine (200 mg.) in MeOH was added CH_3I (10 ml.) and the reaction mixture was heated on a water bath for 2 hr. The solvent and excess CH_3I were evaporated off and trituration with Et_2O gave crystals. Recrystallization from Me_2CO-MeOH afforded 286 mg. of prisms, m.p. 253°. A solution of dendrobine methiodide in MeOH was shaken vigorously with freshly precipitated AgCl. After separation of the precipitate of AgI by filtration, the filtrate was evaporated under reduced pressure at room temperature and an aqueous solution of sodium picrate was added. The precipitated crystals were collected by filtration and recrystallization from MeOH gave 302 mg. of dendrobine methopicrate which melted at 240~242°. *Anal.* Calcd. for $C_{17}H_{28}O_2N^+ \cdot C_6H_2O_7N_3^-$: C, 54.53; H, 5.97; N, 11.06. Found: C, 54.82; H, 5.90; N, 11.08.

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Summary

From the Chinese drug "Chin-Shin-Hu" imported from Hong Kong, two tertiary bases were isolated. One is dendrobine, first isolated by H. Suzuki, *et al.*[2] and the second is a new base which has not previously been reported in the literature, for which the name dendramine is proposed. The water soluble alkaloid was also examined and it was concluded that the quaternary alkaloid found in this drug is the N-methyl dendrobium salt.

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163. Shunsaku Noguchi, Fujiko Nakayama, and Katsura Morita: Aldol Condensation of Corticoids with Formaldehyde. II.*1 21-Hydroxymethylation of Reichstein's Substance S, Dexamethasone and Deoxycorticosterone.

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In continuation of our previous paper,[1] in which we reported the base catalyzed aldol condensation of hydrocortisone and prednisolone with formaldehyde, we now wish to report the condensation of other corticoids, such as Reichstein's substance S, dexamethasone and deoxycorticosterone, with formaldehyde.

When Reichstein's substance S (I) and dexamethasone (II) were treated with aqueous formaldehyde in the presence of sodium acetate as catalyst, the corresponding 21-hydroxymethylated compounds, *i.e.* 21-hydroxymethyl-Reichstein's substance S (III) and 21-hydroxymethyldexamethasone (IV), were obtained. Similarly, treatment of deoxycorticosterone

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*1 This paper constitutes Part XXXI of Takeda Laboratories' series entitled "Steroids"; Part XXX: This Bulletin, **11**, 1235 (1963).

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1) S. Noguchi, K. Morita: This Bulletin, **11**, 1235 (1963).